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A method of tapering SSRI treatment to mitigate withdrawal symptoms

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Abstract

All antidepressant classes are associated with a withdrawal syndrome. SSRI withdrawal syndrome occurs often and can be severe, and may compel patients to re-commence their medication. Although the withdrawal syndrome can be differentiated from recurrence of the underlying disorder, it may also be mistaken for recurrence, leading to long-term unnecessary medication. Authorities currently recommend short tapers, of between two to four weeks, down to therapeutic minimum, or half minimum doses before complete cessation. Studies have demonstrated that these tapers show minimal benefit over abrupt discontinuation, and are often not tolerated by patients. Tapers over months and down to doses significantly lower than minimum therapeutic doses have shown greater success rates. Other medications associated with withdrawal symptoms are tapered to reduce their biological effect at receptors by fixed amounts in order to minimise withdrawal effects. These are exponential tapering programmes which reduce to very small doses. We examined the PET imaging data of serotonin transporter occupancy by SSRIs to demonstrate that hyperbolically reducing doses of SSRI will reduce their effect on serotonin transporter inhibition in a linear manner. We therefore suggest that SSRIs are tapered hyperbolically and slowly to doses much lower than therapeutic minimums, in line with tapering regimes for other medications associated with withdrawal symptoms. Withdrawal symptoms will then be minimised.

SSRI withdrawal ('discontinuation') syndrome

Many medications are associated with a withdrawal syndrome, most commonly those that act on the cardiovascular and central nervous system¹. All major classes of antidepressants – MAOIs, TCAs, SSRIs, and SNRIs – are associated with withdrawal symptoms^{2,3}. The term 'discontinuation syndrome' was coined to refer to this syndrome in antidepressants⁴. The SSRI discontinuation syndrome, as outlined in DSM-V, and captured in the Discontinuation-Emergent Signs and Symptoms (DESS) checklist⁵ is composed of a wide variety of somatic and psychological symptoms (Figure 1).

SSRI withdrawal symptoms can in part resemble the symptoms of anxiety or depression for which the medication was originally given⁶. However, the withdrawal syndrome can be distinguished from a relapse or recurrence of the underlying disorder by its quickness of onset (days rather than weeks)^{3,7,8}, rapid response to re-introduction of the antidepressant (generally within hours, certainly within days)^{3,7,9}, and the presence of somatic and psychological symptoms quite distinct from the original illness (including, dizziness, nausea, and 'shock-like' sensations)^{7,10}. The withdrawal syndrome can be misdiagnosed as depressive recurrence, leading to prolonged treatment for patients who may not require it¹¹⁻¹³, but it is not clear how often this occurs¹⁴.

SSRI withdrawal symptoms occur in many patients, with reported incidence rates varying from 42-100% for paroxetine^{5,15-18}, to 9-77% for fluoxetine^{5,15,17,18}, and median rates of 53.6% for SSRIs across 14 studies that examined antidepressant withdrawal¹³. The incidence and severity appears to be influenced by half-life and receptor affinities, duration and dose of usage, as well as method of tapering, and individual patient characteristics^{3,9}. A recent systematic review identified five studies that evaluated the severity of withdrawal effects and reported that nearly half of participants who had experienced withdrawal effects choosing the most extreme option in the scale offered to them to describe the severity of those effects¹³. The discontinuation period (14 days after cessation) is also associated with a 60% increase in suicide attempts compared with previous users of antidepressants (the increased risk therefore attributed to the process of withdrawal and not to being untreated)¹⁹.

The syndrome can last for significantly longer than the one to two week period¹³, previously suggested⁴. In one study, the syndrome lasted for at least twelve weeks in 25% of patients¹⁸, and in another for at least six weeks in 40% of people²⁰. A third study reported that 86.7% responded that the syndrome had lasted at least two months, 58.6% at least one year, and 16.2% for more than three years²¹. Case reports identify symptoms enduring for a year or longer^{22,23}.

The increasingly long-term use of SSRIs - with nearly half of patients in the UK taking antidepressants for more than two years^{24,25} - arises in part because patients are unwilling to stop due to the aversive nature of the withdrawal syndrome^{24,26}, and a lack of information on how to mitigate the syndrome^{24,26}. Doctors feel that there is not enough guidance on how to proceed with discontinuation²⁴.

Tapering SSRIs

Current guidelines suggest short tapers to avoid withdrawal symptoms. NICE ²⁷, the BAP ¹², MIMS online ²⁸, and UpToDate ²⁹, suggest tapering periods of between two and four weeks, with linear reductions of dose down to minimum therapeutic doses, or half that, before complete cessation. These guides suggest that fluoxetine does not require tapering ²⁹, or that, in high dose, it may be reduced over two weeks ²⁸. Drug manufacturer advice was found to be similarly 'vague and non-specific' according to recent systematic review ³⁰.

Randomised studies show that tapering for up to 14 days either demonstrated no ¹⁶ or minimal ³¹ improvement in withdrawal symptom severity over abrupt discontinuation ³². It has generally been concluded from these studies that longer tapering regimes are required ^{3,33}. Indeed, studies involving longer tapering periods, of months duration, ³⁴⁻³⁶ have demonstrated better outcomes (Table 1). Reduction of paroxetine by 10mg every 2 weeks, lowered withdrawal incidence from 34% to 4.6%, when compared with abrupt discontinuation in one study ³⁴. When patients who experienced withdrawal in this study were recommenced on medication and then tapered at 5mg every 2-4 weeks, withdrawal was successfully avoided ³⁴. In another study patients who withdrew from SSRIs over up to four months had 5.1 DESS events, compared with 11.7 for patients who abruptly discontinued ³⁵.

In another study with paroxetine, patients who withdrew, over an average duration of 38.6 weeks (range two to 197), titrated to the individual, had a 6% incidence withdrawal syndrome, compared with 78% for abrupt discontinuation ³⁶ (Table 1). Tapering strips for antidepressants, which reduce medication to small fractions of minimum therapeutic dose (for example, 0.5mg for paroxetine and citalopram), have shown favourable outcomes: allowing 71% of 1194 patients, 97% of whom had experienced withdrawal previously to discontinue their medication over a median of 2 months ¹⁴. Several case studies also support the improved efficacy of slower tapering ³⁷⁻³⁹. In one instructive case, several months of tapering, down to an average dose of 6.25mg of sertraline per day was required to avoid withdrawal symptoms in one man, whose withdrawal-induced orthostatic hypotension allowed objective measurement ³⁷. These findings have led to one recommendation to reduce paroxetine by 1% of the original dose every three days ⁴⁰.

Two recent large studies confirm that shorter tapering regimes, as currently advised, are not effective. One study found that tapering over 4 weeks was not feasible, with most (60%) patients tapering their medications over 4 months ⁴¹. Another study, employing largely linear reductions, with final dosages equal to minimum therapeutic doses (or half that value) found that only 37% of patients were able to discontinue their medication ⁴². Furthermore, a large study involving 400 patients showed a significantly lower risk of relapse if antidepressants were tapered gradually (greater than 14 days), rather than rapidly (1-7 days) ⁴³.

Neurobiology of withdrawal and its management

Current approaches to mitigate withdrawal symptoms from SSRIs derive from the rationale that tapering SSRIs will extend the period of time over which biological systems are able to

adapt to reductions in available ligand, thus reducing the intensity of withdrawal symptoms^{3,12,33,44}.

Receptors that are activated by a medication may be down-regulated, or exhibit reduced sensitivity⁴⁵. Abrupt removal of medication disturbs the homeostatic equilibrium, creating a circumstance of reduced stimulation, experienced as withdrawal symptoms, often opposite in nature to the original effect of the drug⁴⁵. For example, the withdrawal syndrome from TCAs which show strong anticholinergic actions are typified by cholinergic effects⁴⁶. Adaptation to medication is more likely in the case of long term and high-dose use^{47,48}. Medications with shorter half-lives produce withdrawal symptoms with greater incidence, greater severity and quicker onset than medications with longer half-lives, probably because their withdrawal is associated with more rapid decreases in amount of available ligand^{47,49,50}. Withdrawal symptoms can usually be extinguished by re-introduction of the discontinued agent, returning the system to homeostatic equilibrium⁴⁵.

The principal approach to mitigate withdrawal symptoms is to reduce the rate at which the equilibrium is disturbed, allowing time for adaptation of the system to lowered levels of ligand, thus limiting withdrawal symptoms to tolerable severity⁴⁷. This is achieved either by substitution of a longer acting medication before tapering, or slow tapering (of a drug with a short half-life)^{47,50}.

Notably, decreasing medication by constant amounts (linear tapering) tends to cause increasingly severe side effects^{47,50,51}. This phenomenon is probably a consequence of the hyperbolic dose-response relationship between a drug and receptor, following the law of mass action⁵², as typified by the effect of diazepam on its target receptor, GABA-A (Figure 2a). Consequently, tapering regimes for benzodiazepines advise increasingly small decreases in dosage as dosages approach zero^{47,50,51}, captured epigrammatically as “stop slow as you go low”¹.

Withdrawal regimes for benzodiazepines recommend dosage reductions that are proportional to the current dose (most commonly suggesting 10% reductions), yielding exponentially decreasing regimes, as opposed to linear reductions^{47,51,53} (Figure 2b). These exponentially decreasing regimes produce approximately linear reductions of effect at the target receptor. Reductions are usually made to doses well beneath minimum therapeutic doses (that may appear miniscule) before complete cessation. This is done in order to avoid a step down in action at the target receptor that is significantly greater than the size of steps previously tolerated. For example, the final dose of diazepam recommended by tapering regimes is 1mg⁴⁷ (equivalent to 2% GABA occupancy⁵⁴).

On the premise that withdrawal symptoms abate because of homeostatic adaptations to reduced medication levels, a pause is recommended in between dose reductions^{47,50,51}. However, the exact timing of these adaptations is not fully understood and, therefore, most guidelines for withdrawal have been developed based on clinical experience; a consensus suggests waiting 1-4 weeks in between dose reductions, to allow withdrawal symptoms to resolve^{47,50}. Most guidelines recommend individualisation of this process, given variation in adaptation to change in drug levels, and consequent severity and duration of withdrawal symptoms^{47,50}.

Pharmacological characteristics of SSRI withdrawal

Whether called a withdrawal or discontinuation syndrome, the syndrome that occurs on cessation of SSRIs conforms to the same determinants as other withdrawal syndromes, outlined above. Withdrawal symptoms are more common when SSRIs are given in higher doses^{55,56}, or for longer periods⁵⁵. Medications with shorter half-lives, like paroxetine, produce withdrawal symptoms with greater incidence^{5,15–18}, quicker onset^{5,15–18}, and greater severity^{5,15–18} than medications with longer half-lives, like fluoxetine^{5,15,17,18}. Paroxetine produces withdrawal symptoms within two days⁵⁷, whereas fluoxetine's can be delayed by two⁹ to six weeks²⁰.

As with withdrawal from other medications, the appearance of these withdrawal effects correlate with percentage reductions in plasma concentration⁵⁷. Higher SSRI plasma levels before cessation⁵⁸ and just after cessation⁵⁹ predict increased withdrawal symptoms. Re-introduction of the discontinued antidepressant generally resolves symptoms within 24 hours³. Following the approach to diminishing the withdrawal symptoms from other agents, both tapering of SSRIs^{9,12} and substitution of the longest acting SSRI, fluoxetine,^{3,12} have been trialled. Individual factors, including genetics³⁶, have also been thought to play a role in determining withdrawal effects.

Neurobiology of SSRI withdrawal

SSRIs are thought to produce their effect through an “initiating” step of inhibition of the serotonin transporter (SERT), leading to an increase in synaptic levels of serotonin, thereby transducing increased responses at serotonergic receptors^{60,61}. Serotonergic neurons also modulate other neurotransmitter systems including noradrenaline, dopamine and GABA⁴⁹. Effects on neurogenesis, inflammation, and the HPA axis, downstream of serotonergic actions, are also hypothesised in their antidepressant effects^{60,62,63}. Although the details remain to be elucidated, SSRI withdrawal has been attributed to a relative deficiency of serotonin in the context of widespread adaptation of serotonergic receptors^{9,49,64}. The association of withdrawal symptoms from paroxetine and the C(-1019)G polymorphism of the serotonin 1A receptor (5-HT1A) gene³⁶, a receptor widely implicated in antidepressant action⁶⁰, supports this notion. A role is also postulated for the reversal of effect on neurotransmitters, including noradrenaline, glutamate and GABA, amongst other targets that are indirectly affected by SSRIs^{9,49,64}.

Serotonin's role in coordinating sensory and autonomic function with motor activity has been implicated in the SSRI withdrawal syndrome⁴⁴. Reduced stimulation of raphe 5-HT1A receptors, known to be involved in motion sickness⁴⁹ is thought to be related to the dizziness, vertigo, nausea and lethargy of the withdrawal syndrome⁴⁹; dysregulation of somatosensory functions may result in paraesthesia, while movement disorders (for example, dystonia, sometimes experienced) may be due to altered dopaminergic function⁴⁹.

Pharmacological principles to taper SSRIs

Given the characteristics of the SSRI withdrawal syndrome, the rationale for tapering to reduce withdrawal symptoms is clear. If plasma (and, therefore, tissue) levels of an SSRI drop rapidly, the mismatch between the adapted system and the levels of available ligand will be large and so too the consequent severity of the withdrawal symptoms. Slower tapering of dose or substitution of an SSRI with a longer half-life, such as fluoxetine, will produce more gradual reductions in plasma levels. Akin to other withdrawal syndromes ⁴⁷, neuro-adaptation to lowered levels of available serotonin is likely responsible for resolution of withdrawal symptoms following cessation of an SSRI ^{33,44}. Slower tapering will provide more time for these neuroadaptations and are likely to diminish withdrawal severity ^{33,44,47}.

As with other withdrawal syndromes, a rational tapering regime for SSRIs will entail step-wise reductions of their action at their principal receptor target, SERT ⁶⁰. PET studies, utilising radio-ligand bound to SERT, have demonstrated that the dose-response curve between SSRIs and SERT, conforms to the typical hyperbolic relationship arising as a consequence of the law of mass action (Figure 3). The line of best fit drawn, corresponds to a Michaelis-Menten equation ⁶⁵, applied to such dose-response curves, allows derivation of values for the percentage inhibition of SERT, for different dosages of citalopram (see Figure 3 and Table 2) ⁶¹. Notably, SERT inhibition drops off sharply for doses beneath the minimum therapeutic dose for SSRIs (Table 2).

It is therefore likely that tapering regimes employing linear dose reductions will cause increasingly severe withdrawal reactions, as reductions in SERT inhibition become increasingly large (Figure 4a). For example, reductions of 5mg citalopram increments from 20mg (Figure 4a), will produce hyperbolically increasing-sized decreases to SERT inhibition: 3% (20mg to 15mg), 6% (15mg to 10mg), 13% (10mg to 5mg) and 58% (5mg to 0mg). Indeed, even reductions from 2.5 mg (a quarter of the smallest available tablet) to 0mg will produce a reduction in SERT inhibition of 42.9%, and reduction from 1.25mg (an eighth of a tablet) to 0mg will produce a 28% reduction (larger than the change from 40mg to 5mg (27.3%)), perhaps accounting for the lack of success of previous tapering regimes ^{41,42}, and particularly for the difficulties with withdrawal symptoms experienced by people towards the end of their taper at low doses ^{14,37}.

In order to produce a linear reduction of pharmacological effect, a hyperbolically decreasing pattern of dosage reduction is required (Figure 4b). Rather than decreasing the dose by fixed amounts, the dose should be decreased according to fixed intervals of biological effect, for example, 10% reductions of SERT occupancy (20% reductions shown in Figure 4b). The regime of reduction ensuring approximately 10% SERT occupancy differences between each step for citalopram can be seen in Table 2: 20mg, 9.1mg, 5.4mg, 3.4mg, 2.3mg, 1.5mg, 0.8mg, 0.37mg, 0mg. Appendices show further SSRI examples. These regimes allow pharmacologically-informed application of the withdrawing principles outlined above (“stop slow as you go low”) ^{1,51}. This regime predicts final doses for tapering close to those employed in successful trials involving tapering strips¹⁴, and successfully utilised in case studies involving difficult withdrawal syndromes ³⁷.

Limitations

There are potential limitations to interpretation of the dose-response curve of the PET study presented ⁶¹. The number of participants in each study is relatively small, perhaps limiting its ability to capture individual variation. However, the shape of the dose-response curve (i.e. hyperbolic) should be the same for each individual, suggesting hyperbolic dose reduction regimes should be universally applicable.

There may also be targets of action of SSRIs in addition to the inhibition of SERT and the effect on the serotonergic system, including neurotrophic, anti-inflammatory, and neuroendocrine effects ^{62,63}. However, importantly, these myriad effects are thought to be downstream of effects on SERT and consequent to changes to the serotonergic system ^{60,62,63}, indicating that SERT occupancy is likely to be a key indicator of biological response to SSRIs.

It is difficult to determine whether SERT inhibition will linearly correspond to withdrawal effects. SERT binding is related to the antidepressant effects of SSRIs: the ratio of SERT binding between terminal regions and the median raphe nucleus has been shown to predict treatment response to SSRIs ⁶⁶. It is theoretically possible that a minimum threshold of SERT inhibition is required before clinical effect is seen, with levels lower than this having minimal effects ⁶¹; this may correspond to withdrawal effects as well. However, withdrawal effects from other medications do not observe threshold effects ^{47,50}, and withdrawal effects have been observed at many doses during tapering of SSRIs^{9,36}, suggesting withdrawal is likely to be continuous entity. Furthermore, a hyperbolic relationship exists between dose of SSRI and reduction of depressed mood, as demonstrated in a mega-analysis ⁶⁷; a hyperbolic relationship has also been demonstrated between dose of SSRI and risk of withdrawal symptoms ⁵⁵. These findings suggest that the hyperbolic relationship between dose and SERT inhibition may also be extended to withdrawal effects, suggesting that SERT inhibition may be approximately linearly related to withdrawal effects.

Another potential limitation is that SERT occupancy was measured in the striatum in this study ⁶¹, which may not have direct relevance to antidepressant actions. However, this and a subsequent PET study ⁶⁸ demonstrated that SSRIs cause comparable SERT inhibition in brain regions relevant to SSRI action (subgenual cingulate, amygdala and raphe nuclei), with a similar hyperbolic relationship between dose of SSRI and SERT occupancy at all regions examined ⁶⁸. Overall, it seems reasonable to conclude that SSRIs, like most pharmacological agents, have a hyperbolic relationship to biological effects, and that this may have utility in generating rational discontinuation regimes.

Practical application of these principles

There is likely to be individual differences in each person's experience of SSRI withdrawal effects ³. We suggest that an individualised rate for withdrawal could be established by an initial trial reduction of SSRI dosage equivalent to a reduction of 10% SERT occupancy (or 5% if being cautious), with subsequent monitoring of the severity and duration of withdrawal symptoms. If the patient returned to baseline, on DESS scores, after one month, then a rate equivalent to 10% reduction of SERT occupancy per month could be prescribed. This process should be subject to ongoing monitoring, with the rate titrated to toleration by the patient.

The medication should be tapered to a final dose such that a drop to zero is equal to (or less than) the size of reduction previously tolerated by the patient. Going by ‘the rule of thumb’, this may be when the dose is equivalent to approximately 10% SERT occupancy. Notably, this will be a tiny dose of medication – for example, 0.37mg for citalopram. Interestingly, studies have reported tapering regimes that have only been successful when they taper to similar dosages of SSRIs ^{14,37}. The use of liquid formulations of SSRIs may be necessary to achieve these small dosages.

It is difficult to establish the optimal time interval to observe in between dose reductions. In the absence of studies evaluating the rate at which neuro-adaptation can occur, several aspects can guide us. Pharmacokinetic properties, for all antidepressants, except fluoxetine, predict that they will achieve steady state within 5-14 days after dosage reduction (Table 3) ⁶⁹. As outlined above, discontinuation symptoms have been detected in patients for varying periods of time, from a number of days, to weeks and months, and, in some cases, for more than a year ^{9,22,23,70–72}. These records have generally been derived from patients who abruptly cease their medication; it may be possible that in more cautious reductions discontinuation symptoms are likely to be shorter. The clinical effects of SSRIs may be delayed by weeks following their commencement ^{60 67}, whereas side effects arise in days ⁷³. It is unclear whether withdrawal symptoms are likely to follow the temporal pattern of antidepressant effects, or side effects. Overall, it may be prudent to allow 4 weeks after a reduction in SSRI to observe for delayed side effects. This would also allow for observation of recurrence of underlying symptoms as a result of the decrease in SSRI dose. However, the best guide may be the interval required for DESS symptoms to return to baseline after a test reduction for an individual.

Other determinants of withdrawal symptoms from SSRIs

There are likely to be other drug and patient characteristics that affect the severity of withdrawal syndromes from SSRIs. Paroxetine and fluoxetine are both metabolised by cytochrome P450 2D6 and inhibit their own metabolism, resulting in non-linear kinetics ⁷⁴. This predicts disproportionate declines in plasma concentrations during drug withdrawal. While this effect may not be clinically significant for fluoxetine because of its long half-life, it is likely to be significant for paroxetine ⁴⁹. Paroxetine may produce a more severe withdrawal syndrome than other SSRIs because it has pronounced muscarinic antagonist effects and moderate norepinephrine transporter inhibiting effects ^{49,64}. It is also likely that patient factors such as cytochrome p450 iso-enzyme status, SERT sensitivity to inhibition and psychological factors may contribute to risk of withdrawal symptoms. Further understanding of these factors, and plasma level testing may be instructive in designing personalised tapering regimes.

Some practical consequences of these principles

The model proposed also resolves a quandary often raised by patients and treating physicians: whether to ‘micro-taper’ or ‘mini-taper’. ‘Micro-tapering’ involves miniscule decrements in SSRI medication every day or week. ‘Mini-tapering’ involves step-wise larger decrements, with longer intervals in between decrements (generally, weeks). ‘Mini-tapering’ appears more sensible than ‘micro-tapering’ (although both are linear methods).

Withdrawal symptoms are reported to last for several weeks (or longer) after medication discontinuation in a significant proportion of patients^{9,13}. Given this pattern, ‘micro-tapering’ presents the possibility of cumulative withdrawal effects superimposing upon one another. This would make it difficult to establish which reduction (or set of reductions) were responsible for symptoms experienced. It therefore seems prudent to decrease the dose of medication, allow a significant period of time to elapse while withdrawal effects resolve, before commencing the next decrement.

Fluoxetine

Substitution of short acting SSRIs with fluoxetine has been suggested as a way to avoid intolerable withdrawal symptoms^{3,75}. It has been routinely identified to cause less severe withdrawal effects than other SSRIs, which has been attributed to its longer half-life^{3,30,75}. Fluoxetine should take 35-75 days to reach steady state⁴⁹, a fact that is likely responsible for observations that its withdrawal symptoms can arise weeks after cessation^{9,20}. Therefore, it would be prudent to wait three months (35-75 days plus four weeks), to observe for late arising withdrawal symptoms. Given fluoxetine’s ‘in-built’ tapering it may be reasonable to reduce doses equivalent to approximately 30% SERT occupancy in each iteration, titrated as tolerated by the individual.

We should be wary of the idea that fluoxetine is ‘self-tapering’ and can therefore be abruptly ceased, or ceased rapidly, as guidelines suggest^{30,76}. Although its pharmacokinetic profile predicts gradual plasma level decline, a short reduction (for example, two weeks²⁸), may still represent a rapid withdrawal schedule - more rapid than the 10% of biological effect per month ‘rule of thumb’.

Future directions for research

This paper offers a pharmacologically-informed guide to withdraw from SSRIs. Its validity should be confirmed by randomised controlled trials. Withdrawal nomograms aggregating variation in responses to withdrawal may help guide taper rates (Figure 5). Risk determinants, for example, plasma SSRI level, cytochrome p450 iso-enzyme status, PET measurement of SERT occupancy, and other genetic, metabolic and psychological aspects could be incorporated into this nomogram, as they are clarified. Pharmacological and non-pharmacological means to improve the tolerability of SSRI withdrawal also warrant research^{41,42}.

We suggest that in the absence of more robust evidence for guiding tapering (especially where current guidelines advise to ‘taper gradually’, without concrete instruction) that this regime should be adopted into clinical practice, given little disadvantage to recommending slower tapers³⁰. As a minimum, it should be recognised that tapering periods of 2-4 weeks are likely inadequate for reducing withdrawal symptoms for many, with longer periods of tapering, to lower levels of medication, more likely to be effective. An update of formal guidelines is urgently required.

Contributors

MH conceived the manuscript idea and wrote the manuscript. DT helped develop the idea, and revised and edited the manuscript.

Declaration of Interests

MH declares no conflict of interest.

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